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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/753,892	01/03/2001	Leonid A. Yakubov	PANA-0002	1372

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EXAMINER
PRIEBE, SCOTT DAVID

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/753,892	Yakubov
Examiner	**Art Unit**
Scott D. Priebe, Ph.D.	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 5, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-22 and 31-38* is/are pending in the application.

4a) Of the above, claim(s) *32-38* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-22 and 31* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *6 & 7*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The amendment filed 9/5/02 has been entered. Claims 23-30 have been cancelled. Claims 31-38 have been added.

Election/Restriction

Newly submitted claims 32-38 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

The elected invention originally presented is directed to the treatment of a disease or disorder in an individual where the disease or disorder is associated with genetic mutations or undesirable alleles, i.e. a genetic disease or disorder. The method comprises administering complete genomic DNA comprising the non-mutated sequence or desirable alleles which has been reduced to polynucleotide molecules between 100-3000 nucleotides. The newly presented invention is directed to introducing desired alleles into livestock having an undesired allele by a method comprising administering polynucleotides of 100-3000 nucleotides which include a polynucleotide comprising the desired allele. The newly presented invention differs in two key respects from the elected invention. First, the polynucleotides used are different. In the elected invention, the polynucleotides must represent a complete genome, presumably of another individual of the same species. In the newly presented invention, the polynucleotides do not have to collectively comprise a genome, and the claims embrace using a purified polynucleotide. Second, the goal of the methods are substantially different. The goal, or effect, of the elected

invention is to treat disease, i.e. it is practiced on individuals with a disease. The goal of the newly presented method is to introduce a desired allele, which embraces alleles governing traits that have nothing to do with disease, such as color or texture of hair or fur, size or shape of the livestock, amount of fat in meat, length of legs or tail, etc.

Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different functions and effects.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 32-38 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Information Disclosure Statement

References AF, AG, AK, BB, and BC were considered only with respect to the English abstract.

Claim Objections

Claims 5 and 16-22 are objected to because of the following informalities: In claim 5, recitation of "and/or" is improper grammar. In claims 16-22, "polynucleotide molecule" should be --polynucleotide molecules--. Appropriate correction is required.

Claim Rejections - 35 USC § 101 & 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-22 and 31 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible asserted utility or a well established utility.

Claims 1-22 and 31 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible asserted utility or a well established utility for the reasons set forth below, one skilled in the art clearly would not know how to use the claimed invention.

The invention is directed to a method for treating a genetic disease or disorder in an individual having a mutation associated with the disease or disorder by administering to that individual a collection of polynucleotides of 100-3000 nucleotides which collectively comprise a

complete genome, presumably from an individual who does not have the genetic disease or disorder, wherein some of the polynucleotides contain a non-mutated sequence or desired allele. The claim recites that at least some of the molecules will undergo homologous recombination with cellular genomes, such that a polynucleotide which comprises the non-mutated or desired sequence will replace the mutated or undesired sequence. The specification presents no experimental results which validate the claimed method, and based on the prior art discussed below relating to gene targeting, the claimed method would not have been credible on its face to one of skill in the art.

The invention is based upon the untested hypothesis that circulating genomic DNA arising from apoptosis is used by cells as a guide or template to correct mutations via homologous recombination. It was known that RNA and DNA could be taken up by cells by a saturable, receptor-mediated endocytotic or pinocytotic pathway, with the nucleic acid being predominately located in the cytoplasm, not the nucleus (Bennett, Antisense Res. Dev. 3: 235-241, 1993). Since the pathway is saturable, a cell would be able to take up only a limited amount of DNA. In one study using λ phage DNA, human leukocytes *in vitro* were found to bind approximately 3000 molecules. Of the internalized DNA, 80% was degraded to <12 base pairs. Labeled oligonucleotides administered intravenously or intraperitoneally to mice was found to be degraded and excreted in the urine (30%) or incorporated into kidney, liver and intestine in high molecular weight DNA. Bennett concluded that this pathway was a DNA salvage pathway.

Gene targeting has been studied as a method for gene therapy. Gene targeting involves the correction of a faulty gene by providing a DNA molecule that contains the desired sequence such that it can undergo homologous recombination with the faulty gene and correct the faulty sequence. This strategy differs from gene augmentation or supplementation therapy, which involves delivering a therapeutic gene to a target cell, adding an exogenous gene to the cellular genome rather than correcting a faulty endogenous gene. Yáñez et al. (Gene Ther. 5: 149-159, 1998) reviews the state of therapeutic gene targeting. Unlike the instant invention, prior art gene targeting involves administration to cells of a single polynucleotide molecule that is homologous to the target sequence and contains the desired sequence. Yáñez et al. teach that while gene targeting has been achieved in isolated cells, it has low efficiency and is impractical for *in vivo* use. Gene targeting experiments *in vitro* using a single dsDNA molecule typically yield only 10^{-5} to 10^{-7} targeted cells per cell exposed to DNA. In contrast, gene therapy by gene augmentation or supplementation using viral vectors can result in transfection of greater than 10% of target cells, i.e. it is 10000 to 1000000-fold more efficient at delivering a desired gene to a cell. Also, for every targeted cell obtained *in vitro*, in which homologous recombination occurred, 30 to 40000 cells are obtained in which the DNA molecule is integrated randomly by illegitimate or non-homologous recombination. As a result, the gene targeting method is far more mutagenic than corrective, i.e. for every cell having a corrected mutation (homologous recombination), 30 to 40000 cells will have insertion mutations. The efficiency of gene targeting is also affected by the length of homology present in the DNA molecule used, where efficiency increases exponentially

up to about 14 kb of homology between targeting DNA and target DNA. The claimed method uses DNA molecules with substantially shorter length of homology. The efficiency also depends on the degree of sequence identity between the targeting DNA and the target sequence, with isogenic DNA having the highest efficiency. Yáñez et al. concluded that *in vivo* gene therapy by gene targeting "is not viable at present." See Yáñez at pages 149-150, 156. Riele et al. (Proc. Natl. Acad. Sci. USA, 89: 5128-5132, 1992) observed that using isogenic DNA for gene targeting in mouse ES cells was 20-fold more efficient than DNA from a different mouse strain; however, the use of isogenic DNA did not reduce the level of non-homologous recombination (Abstract; Table 1). With limited exceptions such as in laboratory animals, the instant invention would necessarily involve non-isogenic DNA, especially in humans which in general are highly out-bred.

In a paper published after the instant invention was made, Porter (Molec. Ther. 3 (4): 423-424, 2001) indicates that the main reason that little work is being published in the are of therapeutic gene targeting is the low efficiency, especially in contrast to gene addition therapy with viral vectors, and that the target cells are rare in the body. These factors make gene correction "look like a lost cause." Efforts to improve the efficiency *in vitro* over electroporation by other delivery methods had so far failed to significantly improve the efficiency (page 423). This publication is additional evidence that one of skill in the pertinent art would not have found the claimed invention credible at the time the prophetic invention was made.

As discussed, above DNA binding to cells is saturable. The instant invention involves fragmenting genomic DNA into molecules of between 100-3000 base pairs or nucleotides. Haploid mammalian genomes are approximately 5×10^9 base pairs. If reduced to molecules of 1000 base pairs, the fraction of molecules comprising a single specific base pair, e.g. a mutation site, would be 2×10^{-7} (i.e. $1000 \div 5 \times 10^9$), or one in 5,000,000 molecules. If a mammalian cell binds and takes up 3000 molecules, then the probability that a cell of a population would bind and take up a single molecule having the specific base pair corresponding to a targeted mutation would be 6×10^{-4} (i.e. $3000 \times (2 \times 10^{-7})$). As shown above with isolated DNA targeting constructs, only 10^{-5} to 10^{-7} targeted cells per cell exposed to DNA will have a corrected gene, despite the cells being exposed to a vast excess of the desired replacement sequence. If unfractionated genomic DNA fragments is to be used, as claimed, then the expected gene targeting frequency would be expected to be substantially lower, since DNA binding and uptake by individual cells is saturable (3000 molecules per cell) and the fraction of the genomic fragments that would target a given mutation is about one in 5,000,000 genomic fragments.

Since the prior art just before the instant invention was made shows that one of skill in the art did not believe gene targeting was viable for *in vivo* therapy when a single DNA targeting construct was used, one would not have expected the instant method using unfractionated genomic DNA to be viable either, since it would be expected to be far less efficient than the method taught in the prior art.

The specification reports two experiments alleged to relate to the claimed method. The first involved transfecting human cancer cell lines with fragmented human sperm DNA. In two cell lines the treatment caused reduction in expression of erbB2 and cyclin D1, but no such change was observed in a third cell line. After a time, all cell lines ceased proliferating. In the second experiment, administration of fragmented genomic DNA from one strain of mouse was administered to a second strain of mouse after birth. The treatment allowed establishment of ectopic tumors in the DNA treated mice using a tumor cell line which arose in the first strain. Tumors could not be established in untreated mice of the second strain. While it may be attractive to speculate that these results are explained by homologous recombination between the DNA fragments and the cellular genome, no evidence is provided that homologous recombination-mediated genomic changes were in any way responsible for the results observed. Given the low frequency of gene targeting observed with isolated targeting constructs and the even lower expected frequency using unfractionated genomic fragments, it is unlikely that homologous recombination is responsible. It would be at least as likely to conclude that the known non-homologous recombination that predominates in gene targeting, i.e. random insertion of DNA fragments, is responsible for the observed effects since such insertions are mutations and have the potential to exert a phenotypic effect. Alternatively, the effects may have nothing to do with recombination, whether homologous or non-homologous. Gilchrest et al., (US 5,470,577, Ref. BG) showed that liposomal delivery of fragmented salmon sperm DNA to a murine melanoma cell line caused an increase in melanin production (col. 3-4). Gilchrest does not teach

what mechanism is responsible for this effect, however, it is unlikely to be due to homologous recombination between the non-homologous salmon sperm DNA and the murine cell's genomic DNA. Gilchrest speculates that the DNA fragments may trigger an SOS-like response in mammalian cells, similar to that of bacteria, leading to expression of certain genes (col. 1, lines 36-43). Neither of the experiments demonstrate that the source of the DNA mattered, for example would salmon sperm DNA have achieved the same results. Thus, while the disclosed experimental results are provocative, they do not support the invention which is being claimed which requires that phenotypic effects be due to correcting mutations or alleles by homologous recombination.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX numbers are (703) 308-4242 or (703) 305-3014 for any type of communication. In addition, FAX numbers for a computer server system using RightFAX are also available for communications before final rejection, (703) 872-9306, and for communications after final rejection, (703) 872-9307, which will generate a return receipt. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on Monday through Friday from 8 AM to 4 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

Any inquiry concerning administrative, procedural or formal matters relating to this application should be directed to Patent Analyst Patsy Zimmerman whose telephone number is (703) 308-8338. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER